Term	Documents
CD40L.DWPI,EPAB,JPAB.	54
CD40LS	0
CD40.DWPI,EPAB,JPAB.	197
CD40S	0
LIGAND.DWPI,EPAB,JPAB.	23137
LIGANDS.DWPI,EPAB,JPAB.	10319
GP39.DWPI,EPAB,JPAB.	41
GP39S	0
ANTIBOD$	0
ANTIBOD.DWPI,EPAB,JPAB.	47
((CD40L OR CD40 ADJ LIGAND OR GP39) SAME (ANTIBOD$) AND (OOPHORITIS OR THYROIDITIS)).JPAB,EPAB,DWPI.	4

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L3: Entry 59 of 61 File: USPT Oct 15, 1996

DOCUMENT-IDENTIFIER: US 5565491 A
TITLE: Use of phosphotyrosine phospatase inhibitors for controlling cellular proliferation

Detailed Description Paragraph Right (56):
However, phosphotyrosine phosphatase inhibitors can also be used to control proliferation of normal B cells, particularly in situations in which downregulation of the immune response is desired. Such situations include induction of immunosuppression to prevent transplant rejection, as well as in the treatment of autoimmune diseases such as rheumatoid arthritis, Hashimoto's thyroiditis, and systemic lupus erythematosus, as well as other autoimmune diseases.

Detailed Description Paragraph Right (66):
Methods according to the present invention can also be used to inhibit phosphotyrosine phosphatases for purposes other than that of treating malignant disease. In particular, phosphotyrosine phosphatase inhibitors can be used to suppress the immune system in order to prevent organ or tissue rejection during transplantation and also in the treatment of autoimmune diseases such as rheumatoid arthritis, Hashimoto's thyroiditis, systemic lupus erythematosus, Guillain-Barre Syndrome, and possibly multiple sclerosis.

Detailed Description Paragraph Right (69):
Methods according to the present invention can further be used to prevent class-switching in antibodies from IgG or IgM to IgE. It is desirable to block IgE production because this type of antibody mediates many allergic responses, particularly immediate-type hypersensitivity reactions such as anaphylaxis, atopy, and urticaria. The CD40 ligand gp39 and the cytokine IL-4act on B cells to induce the switching of the type of antibody produced from IgM to IgE. CD40 and IL-4 mechanisms of action are known to involve tyrosine phosphorylation. Phosphotyrosine phosphatase inhibitors such as BMLOV disrupt the normal pattern of tyrosine phosphorylation, disrupting the class-switching process. The administration of BMLOV, in particular, can markedly inhibit the production of IgE antibody while much less markedly inhibiting the production of IgG subclasses such as IgG1 and IgG4. This leads to the result that the ratio of IgG to IgE increases (Example 14). This result leads to the conclusion that phosphotyrosine phosphatase inhibitors such as BMLOV have value in the treatment of allergy.

Detailed Description Paragraph Right (88):
BMLOV can inhibit normal tonsillar B cell proliferation driven by stimulation of CD40 via either anti-CD40 antibody or gp39 ligand plus either anti-CD20 antibody or phorbol 12-myristate 13-acetate (PMA). In one experiment, doses of 0.1 to 10 .mu.M had little effect on proliferation (FIG. 3). In a second experiment, a dose of 5 .mu.M gave substantial inhibition of proliferation and a dose of 50 .mu.M completely blocked proliferation (FIG. 4). Variations between the individuals from which the tonsils were derived could account for the differences between these experiments.

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L3: Entry 60 of 61 File: USPT May 28, 1996

DOCUMENT-IDENTIFIER: US 5521315 A
TITLE: Olefin substituted long chain compounds

Detailed Description Paragraph Right (17):
The inventive compounds inhibit signal transduction mediated through the Type I IL-1 receptor, and are therefore considered as IL-1 antagonists. A recent review article entitled "The Role of interleukin-1 in Disease" (Dinarello and Wolff N. Engl. J. Med. 328, 106, Jan. 14, 1993) described the role of IL-1 as "an important rapid and direct determinant of disease." "In septic shock, for example, IL-1 acts directly on the blood vessels to induce vasodilatation through the rapid production of platelet activating factor and nitric oxide, whereas in autoimmune disease it acts by stimulating other cells to produce cytokines or enzymes that then act on the target tissue." The article describes a group of diseases that are mediated by IL-1, including sepsis syndrome, rheumatoid arthritis, inflammatory bowel disease, acute and myelogenous leukemia, insulin-dependent diabetes mellitus, atherosclerosis and other diseases including transplant rejection, graft versus host disease (GVHD), psoriasis, asthma, osteoporosis, periodontal disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secondary to uterine infection and even sleep disorders. Since the inventive compounds inhibit cellular signaling through the IL-1 Type I receptor and are IL-1 antagonists, the inventive compounds are useful for treating all of the above-mentioned diseases.

Detailed Description Paragraph Right (29):
The compounds of the invention provide a mechanism to maintain homeostasis in cells contacted by primary stimuli through mitigating the effects of these primary stimuli on the secondary signaling pathways invoked within seconds of the primary stimulus. For example, administration of the inventive compounds in vivo or ex vivo provide a method to modify cellular behavior which method comprises contacting cells (in vivo or ex vivo) whose behavior is to be modified with an effective amount of an inventive compound or a pharmaceutical composition thereof wherein said method is: (1) a method to inhibit proliferation of tumor cells and said amount is sufficient to inhibit said proliferation; or (2) a method to promote differentiation of hematopoietic stem cells into red blood cells, platelets, lymphocytes, and granulocytes, and said amount is sufficient to promote said proliferation; or (3) a method to suppress activation of T-cells by antigen or IL-2 stimulation, and said amount is sufficient to promote said activation; or (4) a method to suppress activation of monocyte/macrophage cells by endotoxin, TNF, IL-1 or GM-CSF stimulation and said amount is sufficient to suppress said activation; or (5) a method to enhance the resistance of mesenchymal cells to the cytotoxic effect of tumor necrosis factor and said amount is sufficient to enhance said resistance; or (6) a method to suppress antibody production of B-cells in response to an antigen, IL-4 or CD40 ligand and said amount is sufficient to suppress said antibody production; or (7) a method to inhibit the proliferation of smooth muscle cells in response to growth factors capable of stimulating said proliferation and said amount is sufficient to inhibit said proliferation; or (8) a method to lower systemic vascular resistance conferred by endothelial cells and said amount is sufficient to reduce the release of hypertension-inducing substances; or (9) a method to lower systemic vascular resistance induced by endothelial cells and said amount is sufficient to enhance the release of anti-hypertensive substances; or (10) a method to lower expression of adhesion molecules induced by enhancers thereof, and said amount is sufficient to lower said expression; or (11) a method to suppress the activation of T-cells by HIV and said amount is sufficient to suppress said activation thus inhibiting viral replication; or (12) a method to inhibit the

proliferation of kidney mesangial cells in response to stimulation by IL-1 and/or Mip-1.alpha. and/or PDGF and/or FGF and said amount is sufficient to inhibit said proliferation; or (13) a method to enhance the resistance of kidney glomerular or tubular cells to cyclosporin A or amphotericin B and said amount is sufficient to enhance said resistance; or (14) a method to prevent the suppression of growth stimulatory factor production in TNF-treated bone marrow stromal cells and said amount is sufficient to prevent said suppression; or (15) a method to prevent the release of Mip-1.alpha. by IL-1, TNF, or endotoxin stimulated monocytes and macrophages; or (16) a method to prevent the release of platelet activating factor by IL-1, TNF, or endotoxin treated megakaryocytes, fibroblastic cells, and macrophages; or (17) a method to prevent the down-regulation of receptors for cytokines in TNF-treated hematopoietic progenitor cells and said amount is sufficient to prevent said down-regulation; or (18) a method to suppress the production of metalloproteases in IL-1-stimulated or TNF-stimulated glomerular epithelial cells or synovial cells and said amount is sufficient to enhance said production; or (19) a method to enhance the resistance of gastrointestinal or pulmonary epithelial cells to cytotoxic drugs or radiation and said amount is sufficient to enhance said resistance; or (20) a method to enhance the antitumor effect of a non-alkylating antitumor agent and said amount is sufficient to enhance said effect, or (21) a method to inhibit the production of osteoclast activating factor in response to IL-1, and said amount is sufficient to inhibit said production, or (22) a method to inhibit degranulation in response to IgE, and said amount is sufficient to inhibit said degranulation, or (23) a method to enhance the release of adrenergic neural transmitters, dopamine, norepinephrine, or epinephrine, or the neurotransmitter, acetylcholine, and said amount is sufficient to enhance said release, or (24) a method to modulate the post-synaptic "slow current" effects of the adrenergic neurotransmitters dopamine, epinephrine, or norepinephrine, or the neurotransmitter acetylcholine, and said amount is sufficient to modulate such slow currents.

Detailed Description Paragraph Right (52):
The compounds of the invention provide a mechanism to maintain homeostasis in cells contacted by primary stimuli through mitigating the effects of these primary stimuli on the secondary signaling pathways invoked within seconds of the primary stimulus. For example, administration of the inventive compounds in vivo or ex vivo provide a method to modify cellular behavior which method comprises contacting cells (in vivo or ex vivo) whose behavior is to be modified with an effective amount of an inventive compound or a pharmaceutical composition thereof wherein said method is: (1) a method to inhibit proliferation of tumor cells and said amount is sufficient to inhibit said proliferation; or (2) a method to promote differentiation of hematopoietic stem cells into red blood cells, platelets, lymphocytes, and granulocytes, and said amount is sufficient to promote said proliferation; or (3) a method to suppress activation of T-cells by antigen or IL-2 stimulation, and said amount is sufficient to promote said activation; or (4) a method to suppress activation of monocyte/macrophage cells by endotoxin, TNF, IL-1 or GM-CSF stimulation and said amount is sufficient to suppress said activation; or (5) a method to enhance the resistance of mesenchymal cells to the cytotoxic effect of tumor necrosis factor and said amount is sufficient to enhance said resistance; or (6) a method to suppress antibody production of B-cells in response to an antigen, IL-4 or CD40 ligand and said amount is sufficient to suppress said antibody production; or (7) a method to inhibit the proliferation of smooth muscle cells in response to growth factors capable of stimulating said proliferation and said amount is sufficient to inhibit said proliferation; or (8) a method to lower systemic vascular resistance conferred by endothelial cells and said amount is sufficient to reduce the release of hypertension-inducing substances; or (9) a method to lower systemic vascular resistance induced by endothelial cells and said amount is sufficient to enhance the release of anti-hypertensive substances; or (10) a method to lower expression of adhesion molecules induced by enhancers thereof, and said amount is sufficient to lower said expression; or (11) a method to suppress the activation of T-cells by HIV and said amount is sufficient to suppress said activation thus inhibiting viral replication; or (12) a method to inhibit the proliferation of kidney mesangial cells in response to stimulation by IL-1 and/or Mip-1.alpha. and/or PDGF and/or FGF and said amount is sufficient to inhibit said proliferation; or (13) a method to enhance the resistance of kidney glomerular or tubular cells to cyclosporin A or amphotericin B and said amount is sufficient to

enhance said resistance; or (14) a method to prevent the suppression of growth stimulatory factor production in TNF-treated bone marrow stromal cells and said amount is sufficient to prevent said suppression; or (15) a method to prevent the release of Mip-1.alpha. by IL-1, TNF, or endotoxin stimulated monocytes and macrophages; or (16) a method to prevent the release of platelet activating factor by IL-1, TNF, or endotoxin treated megakaryocytes, fibroblastic cells, and macrophages; or (17) a method to prevent the down-regulation of receptors for cytokines in TNF-treated hematopoietic progenitor cells and said amount is sufficient to prevent said down-regulation; or (18) a method to suppress the production of metalloproteases in IL-1-stimulated or TNF-stimulated glomerular epithelial cells or synovial cells and said amount is sufficient to enhance said production; or (19) a method to enhance the resistance of gastrointestinal or pulmonary epithelial cells to cytotoxic drugs or radiation and said amount is sufficient to enhance said resistance; or (20) a method to enhance the antitumor effect of a non-alkylating antitumor agent and said amount is sufficient to enhance said effect, or (21) a method to inhibit the production of osteoclast activating factor in response to IL-1, and said amount is sufficient to inhibit said production, or (22) a method to inhibit degranulation in response to IgE, and said amount is sufficient to inhibit said degranulation, or (23) a method to enhance the release of adrenergic neural transmitters, dopamine, norepinephrine, or epinephrine, or the neurotransmitter, acetylcholine, and said amount is sufficient to enhance said release, or (24) a method to modulate the post-synaptic "slow current" effects of the adrenergic neurotransmitters dopamine, epinephrine, or norepinephrine, or the neurotransmitter acetylcholine, and said amount is sufficient to modulate such slow currents.

Set Name side by side	Query	Hit Count	Set Name result set
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L4	(cd40L or cd40 adj ligand or gp39) same (antibod$) and (oophoritis or thyroiditis)	4	L4
	DB=USPT,PGPB; PLUR=YES; OP=ADJ		
L3	(cd40L or cd40 adj ligand or gp39) same (antibod$) and (oophoritis or thyroiditis)	61	L3
L2	(cd40L or cd40 adj ligand or gp39) same (antibod$) and (diabetes or oophoritis or thyroiditis)	96	L2
L1	(cd40L or cd40 adj ligand or antibod$) same (antibod$) and (diabetes or oophoritis or thyroiditis)	7368	L1

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GP39S	0
ANTIBOD$	0
ANTIBOD.DWPI,EPAB,JPAB.	47
ANTIBODANTIBODA.DWPI,EPAB,JPAB.	1
((CD40L OR CD40 ADJ LIGAND OR GP39) SAME (ANTIBOD$) AND (OOPHORITIS OR THYROIDITIS)).JPAB,EPAB,DWPI.	4

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Search Results - Record(s) 1 through 4 of 4 returned.

☐ 1. Document ID: HU 200102101 A2, WO 9924035 A1, AU 9913719 A, NO 200002121 A, EP 1037632 A1, ZA 9810219 A, BR 9814956 A, CZ 200001717 A3, CN 1290165 A, KR 2001031912 A, MX 2000003266 A1, JP 2001522800 W

L4: Entry 1 of 4 File: DWPI Nov 28, 2001

DERWENT-ACC-NO: 1999-457860
DERWENT-WEEK: 200209
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TITLE: New protein tyrosine kinase inhibiting benzothiazole derivatives

INVENTOR: BARRISH, J C; DAS, J ; WITYAK, J

PRIORITY-DATA: 1997US-065042P (November 10, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
HU 200102101 A2	November 28, 2001		000	C07D277/82
WO 9924035 A1	May 20, 1999	E	220	A61K031/425
AU 9913719 A	May 31, 1999		000	
NO 200002121 A	May 9, 2000		000	A61K000/00
EP 1037632 A1	September 27, 2000	E	000	A61K031/425
ZA 9810219 A	August 30, 2000		222	C07D000/00
BR 9814956 A	October 3, 2000		000	A61K031/425
CZ 200001717 A3	October 11, 2000		000	C07D277/82
CN 1290165 A	April 4, 2001		000	A61K031/425
KR 2001031912 A	April 16, 2001		000	A61K031/425
MX 2000003266 A1	November 1, 2000		000	A61K031/425
JP 2001522800 W	November 20, 2001		309	C07D277/82

INT-CL (IPC): A61 K 0/00; A61 K 31/425; A61 K 31/428; A61 K 31/429; A61 K 31/44; A61 K 31/4439; A61 K 31/445; A61 K 31/454; A61 K 31/47; A61 K 31/4709; A61 K 31/498; A61 K 31/50; A61 K 31/501; A61 K 31/505; A61 K 31/535; A61 K 31/5377; A61 K 31/55; A61 P 1/04; A61 P 7/06; A61 P 9/10; A61 P 11/02; A61 P 11/06; A61 P 13/12; A61 P 17/00; A61 P 17/06; A61 P 17/14; A61 P 19/02; A61 P 29/00; A61 P 37/00; A61 P 37/06; A61 P 37/08; A61 P 43/00; C07 D 0/00; C07 D 277/82; C07 D 401/06; C07 D 407/06; C07 D 409/06; C07 D 413/06 ; C07 D 417/06; C07 D 417/12; C07 D 471/04; C07 D 513/10; C07 F 0/00

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Clip Img | Image

☐ 2. Document ID: WO 9909845 A1, AU 9886817 A, ZA 9807649 A, US 6235740 B1

L4: Entry 2 of 4 File: DWPI Mar 4, 1999

DERWENT-ACC-NO: 1999-190409
DERWENT-WEEK: 199916
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TITLE: New imidazoquinoxaline compounds inhibit protein tyrosine kinases - used to treat e.g. immunological disorders

INVENTOR: BARRISH, J C; CHEN, P ; DAS, J ; IWANOWICZ, E J ; NORRIS, D J ; PADMANABHA, R ; ROBERGE, J Y ; SCHIEVEN, G L

PRIORITY-DATA: 1997US-069159P (December 9, 1997), 1997US-056770P (August 25, 1997), 1998US-0097338 (June 15, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 9909845 A1	March 4, 1999	E	315	A61K031/54
AU 9886817 A	March 16, 1999		000	C07D403/02
ZA 9807649 A	April 26, 2000		353	C07D000/00
US 6235740 B1	May 22, 2001		000	C07D487/04

INT-CL (IPC): A61 K 31/4745; A61 K 31/495; A61 K 31/54; C07 D 0/00; C07 D 403/02; C07 D 413/14; C07 D 487/04; C07 F 0/00

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments

KWIC | Draw Desc | Clip Img | Image

☐ 3. Document ID: KR 99067370 A, WO 9717446 A2, AU 9711576 A, WO 9717446 A3, NO 9802062 A, EP 862630 A2, CN 1207127 A, NZ 324500 A, HU 9902327 A2, US 6001358 A, JP 2000500334 W, AU 717762 B

L4: Entry 3 of 4 File: DWPI Aug 16, 1999

DERWENT-ACC-NO: 1997-281035
DERWENT-WEEK: 200045

TITLE: Humanised antibody capable of competing with, or derived from, murine 24-31 antibody - useful to modulate gp39 expression or inhibiting gp39/CD40 interaction

INVENTOR: BLACK, A; HANNA, N ; NEWMAN, R A ; PADLAN, E A

PRIORITY-DATA: 1995US-0554840 (November 7, 1995)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
KR 99067370 A	August 16, 1999		000	C12N015/13
WO 9717446 A2	May 15, 1997	E	106	C12N015/13
AU 9711576 A	May 29, 1997		000	C12N015/13
WO 9717446 A3	September 25, 1997		000	C12N015/13
NO 9802062 A	July 6, 1998		000	C07K000/00
EP 862630 A2	September 9, 1998	E	000	C12N015/13
CN 1207127 A	February 3, 1999		000	C12N015/13
NZ 324500 A	August 28, 1999		000	C07K016/46
HU 9902327 A2	October 28, 1999		000	C12N015/13
US 6001358 A	December 14, 1999		000	A61K039/395
JP 2000500334 W	January 18, 2000		098	C12N015/09
AU 717762 B	March 30, 2000		000	C12N015/13

INT-CL (IPC): A61 K 39/395; A61 P 1/04; A61 P 3/10; A61 P 11/06; A61 P 17/00; A61 P 17/06; A61 P 27/00; A61 P 29/00; A61 P 35/02; A61 P 37/00; A61 P 37/08; C07 K 0/00; C07 K 16/28; C07 K 16/46; C12 N 15/09; C12 N 15/13; C12 N 15/09; C12 R 1:91

☐ 4. Document ID: US 2002009450 A1, WO 9640246 A1, AU 9662559 A, ZA 9604851 A, NO 9705520 A, EP 831906 A1, US 5833987 A, AU 705623 B, JP 11507058 W, HU 9900857 A2, BR 9706397 A, KR 99022273 A, NZ 311276 A, MX 9709670 A1, EP 1161954 A1, US 6328964 B1

L4: Entry 4 of 4 File: DWPI Jan 24, 2002

DERWENT-ACC-NO: 1997-108629
DERWENT-WEEK: 200210

TITLE: Treating or preventing T cell mediated disorder with antibody to T cell surface receptor - that mediates contact-dependent helper effector function, esp. for multiple sclerosis

INVENTOR: CLAASSEN, E; NOELLE, R J ; CLASSEN, E ; NOELLE, R H

PRIORITY-DATA: 1995US-0481735 (June 7, 1995), 1997BR-0006397 (December 19, 1997), 1998US-0080349 (May 18, 1998), 2001US-0849969 (May 8, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 2002009450 A1	January 24, 2002		000	A61K039/395
WO 9640246 A1	December 19, 1996	E	022	A61K039/395
AU 9662559 A	December 30, 1996		000	A61K039/395
ZA 9604851 A	September 23, 1997		018	A61K000/00
NO 9705520 A	February 6, 1998		000	A61K000/00
EP 831906 A1	April 1, 1998	E	000	A61K039/395
US 5833987 A	November 10, 1998		000	A61K039/395
AU 705623 B	May 27, 1999		000	A61K039/395
JP 11507058 W	June 22, 1999		028	A61K039/395
HU 9900857 A2	July 28, 1999		000	A61K039/395
BR 9706397 A	October 5, 1999		000	A61K039/395
KR 99022273 A	March 25, 1999		000	A61K039/395
NZ 311276 A	November 29, 1999		000	A61K039/395
MX 9709670 A1	July 1, 2000		000	A61K039/395
EP 1161954 A1	December 12, 2001	E	000	A61K039/395
US 6328964 B1	December 11, 2001		000	A61K039/395

INT-CL (IPC): A61 K 0/00; A61 K 39/395; A61 K 45/00; A61 P 37/06; C07 K 16/28; C12 N 0/00; C12 P 21/08; G01 N 0/00; C12 P 21/08; C12 R 1:91

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Term	Documents
THYROIDITIS.USPT,PGPB.	1652
THYROIDITI	0
OOPHORITIS.USPT,PGPB.	41
OOPHORITI	0
INHIBIT$	0
INHIBIT.USPT,PGPB.	164256
INHIBITA.USPT,PGPB.	1
INHIBITABILITIES.USPT,PGPB.	2
INHIBITABILITY.USPT,PGPB.	55
INHIBITABILITY-THE.USPT,PGPB.	1
"INHIBITABILITY>".USPT,PGPB.	2
. . . . .	
BLOCK$(BLOCKS/RECESSES).USPT,PGPB.	pickup term
. . . . .	
ANTIBOD$(ANTIBODY-URPOLYPEPTIDE).USPT,PGPB.	pickup term
((THYROIDITIS OR OOPHORITIS) SAME (INHIBIT$ OR SUPPRESS$ OR BLOCK$ OR ANTAGONI$) SAME (ANTIBOD$) SAME ('T-CELL' OR 'T-LYMPHOCYTE')).USPT,PGPB.	29

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Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB; PLUR=YES; OP=ADJ			
L9	(thyroiditis or oophoritis) same (inhibit$ or suppress$ or block$ or antagoni$) same (antibod$) same ('t-cell' or 't-lymphocyte')	29	L9
L8	(oophoritis or nephritis) same (autoimmun$) same (inhibit$ or suppress$ or prevent$ or antagoni$) and (antibod$)	235	L8
DB=USPT; PLUR=YES; OP=ADJ			
L7	(oophoritis or nephritis) same (autoimmun$)	626	L7
L6	5833987.pn.	1	L6
L5	6328964.pn.	1	L5
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L4	(cd40L or cd40 adj ligand or gp39) same (antibod$) and (oophoritis or thyroiditis)	4	L4
DB=USPT,PGPB; PLUR=YES; OP=ADJ			
L3	(cd40L or cd40 adj ligand or gp39) same (antibod$) and (oophoritis or thyroiditis)	61	L3
L2	(cd40L or cd40 adj ligand or gp39) same (antibod$) and (diabetes or oophoritis or thyroiditis)	96	L2
L1	(cd40L or cd40 adj ligand or antibod$) same (antibod$) and (diabetes or oophoritis or thyroiditis)	7368	L1

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L9: Entry 23 of 29 File: USPT Nov 5, 1996

DOCUMENT-IDENTIFIER: US 5571499 A
TITLE: Treatment of autoimmune diseases by aerosol administration of autoantigens

Detailed Description Paragraph Right (15):
The present invention may be used to treat a wide variety of autoimmune diseases, both antibody- and cell-mediated. As shown below in Examples 6 and 7, aerosol administration of an autoantigen (guinea pig MBP) and disease-suppressive fragments thereof caused suppression of both cell(e.g. delayed-type hypersensitivity reactions) and antibody-mediated immune responses. In addition, as shown in the data presented in Example 3, this suppression was actively mediated by spleen cells, implying a role for active cellular suppression in this phenomenon. Therefore, as in the case of immune suppression mediated by the oral administration of autoantigens (disclosed in U.S. patent application Ser. No. 65,734 and the copending International Patent Application PCT/US88/02139), aerosol administration of autoantigens is believed to act, at least in part, by mediating the activity of suppressor T-cells. Non-limiting examples of autoimmune diseases which are cell-mediated include multiple sclerosis, rheumatoid arthritis, autoimmune uveoretinitis, diabetes and autoimmune thyroiditis. Antibody-mediated autoimmune diseases include myasthenia gravis, systemic lupus erythematosus (SLE), pemphigus and thrombic thrombocytopenic purpuria. A non-limiting list of disease models and the specific autoantigens effective in the treatment of these diseases when administered in an aerosol form are set forth below in Table 1.

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INHIBIT$	0
INHIBIT.USPT,PGPB.	164256
INHIBITA.USPT,PGPB.	1
INHIBITABILITIES.USPT,PGPB.	2
INHIBITABILITY.USPT,PGPB.	55
INHIBITABILITY-THE.USPT,PGPB.	1
"INHIBITABILITY>".USPT,PGPB.	2
. . . . .	
BLOCK$(BLOCKS/RECESSES).USPT,PGPB.	pickup term
. . . . .	
ANTIBOD$(ANTIBODY-URPOLYPEPTIDE).USPT,PGPB.	pickup term
((THYROIDITIS OR OOPHORITIS) SAME (INHIBIT$ OR SUPPRESS$ OR BLOCK$ OR ANTAGONI$) SAME (ANTIBOD$) SAME ('T-CELL' OR 'T-LYMPHOCYTE')).USPT,PGPB.	29

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Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB; PLUR=YES; OP=ADJ			
L9	(thyroiditis or oophoritis) same (inhibit$ or suppress$ or block$ or antagoni$) same (antibod$) same ('t-cell' or 't-lymphocyte')	29	L9
L8	(oophoritis or nephritis) same (autoimmun$) same (inhibit$ or suppress$ or prevent$ or antagoni$) and (antibod$)	235	L8
DB=USPT; PLUR=YES; OP=ADJ			
L7	(oophoritis or nephritis) same (autoimmun$)	626	L7
L6	5833987.pn.	1	L6
L5	6328964.pn.	1	L5
DB=JPAB,EPAB,DWPI; PLUR=YES; OP=ADJ			
L4	(cd40L or cd40 adj ligand or gp39) same (antibod$) and (oophoritis or thyroiditis)	4	L4
DB=USPT,PGPB; PLUR=YES; OP=ADJ			
L3	(cd40L or cd40 adj ligand or gp39) same (antibod$) and (oophoritis or thyroiditis)	61	L3
L2	(cd40L or cd40 adj ligand or gp39) same (antibod$) and (diabetes or oophoritis or thyroiditis)	96	L2
L1	(cd40L or cd40 adj ligand or antibod$) same (antibod$) and (diabetes or oophoritis or thyroiditis)	7368	L1

END OF SEARCH HISTORY

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End of Result Set

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L2: Entry 96 of 96 File: USPT Nov 28, 1995

DOCUMENT-IDENTIFIER: US 5470878 A
TITLE: Cell signaling inhibitors

Brief Summary Paragraph Right (17):
A disease state or treatment-induced toxicity are selected from the group consisting of: tumor progression involving tumor stimulation of blood supply (angiogenesis) by production of fibroblst growth factor (FGF), vascular endothelial growth factor (VEGF) or platelet-derived growth factor (PDGF); tumor invasion and formation of metastases through adhesion molecule binding, expressed by vascular endothelial cells (VCAM and ICAM); tissue invasion through tumor metalloprotease production such as MMP-9; autoimmune diseases caused by dysregulation of the T cell or B cell immune systems, treatable by suppression of the T cell or B cell responses; acute allergic reactions including, but not limited to, asthma and chronic inflammatory diseases, mediated by pro-inflammatory cytokines including tumor necrosis factor (TNF) and IL-1, and rheumatoid arthritis, osteoarthritis, multiple sclerosis or insulin dependent diabetes mellitus (IDDM), associated with enhanced localization of inflammatory cells and relase of inflammatory cytokines and metalloproteases; smooth muscle cell, endothelial cell, fibroblast and other cell type proliferation in response to growth factors, such as PDGF-AA, BB, FGF, EGF, etc. (i.e., atherosclerosis, restenosis, stroke, and coronary artery disease); activation of human immunodeficiency virus infection (AIDS and AIDS related complex); HIV-associated dementia; kidney mesangial cell proliferation in response to IL-1, MIP-1.alpha., PDGF or FGF; intimation; kidney glomerular or tubular toxicity in response to cyclosporin A or amphotericin B treatment; organ toxicity (e.g., gastrointestinal or pulmonary epithelial) in response to a cytotoxic therapy (e.g., cytotoxic drug or radiation); effects of non-alkylating anti-tumor agents; inflammation in response to inflammatory stimuli (e.g., TNF, IL-1 and the like) characterized by production of metalloproteases or allergies due to degranulation of mast cells and basophils in response to IgE or RANTES; bone diseases caused by overproduction of osteoclast-activating factor (OAF) by osteoclasts; CNS diseases resulting from over-stimulation by pro-inflammatory neurotransmitters such as, acetylcholine, serotonin, leuenkephalin or glutamate; acute inflammatory diseases such as septic shock, adult respiratory distress syndrome; multi-organ dysfunction associated with inflammatory cytokine cascade; and combinations thereof.

Detailed Description Paragraph Right (16):
The inventive compounds inhibit signal transduction mediated through the Type I IL-1 receptor, and are therefore considered as IL-1 antagonists. A recent review article entitled "The Role of Interleukin-1 in Disease" (Dinarello et al., N. Engl. J. Med. (1993) 106:328) described the role of IL-1 as "an important rapid and direct determinant of disease." "In septic shock, for example, IL-1 acts directly on the blood vessels to induce vasodilatation through the rapid production of platelet activating factor and nitric oxide, whereas in autoimmune disease it acts by stimulating other cells to produce cytokines or enzymes that then act on the target tissue." The article describes a group of diseases that are mediated by IL-1, including sepsis syndrome, rheumatoid arthritis, inflammatory bowel disease, acute and myelogenous leukemia, insulin-dependent diabetes mellitus, atherosclerosis and other diseases including transplant rejection, graft versus host disease (GVHD), psoriasis, asthma, osteoporosis, periodontal disease, autoimmune thyroiditis, alcoholic hepatitis, premature labor secondary to uterine infection and even sleep disorders. Since the inventive compounds inhibit cellular signaling through the IL-1

Type I receptor and are IL-1 antagonists, the inventive compounds are useful for treating all of the above-mentioned diseases.

Detailed Description Paragraph Right (21):
Insulin-dependent diabetes mellitus (IDDM) is considered to be an autoimmune disease with destruction of beta cells in the islets of Langerhans mediated by immunocompetent cells. Islets of animals with spontaneously occurring IDDM (e.g., BB rats or NOD mice) have inflammatory cells that contain IL-1. Therefore, the inventive compounds should be useful for the prevention of and treatment of IDDM.

Detailed Description Paragraph Right (28):
The inventive compounds provide a method for maintaining homeostasis in cells contacted by primary stimuli by mitigating the effects of these primary stimuli on the secondary signaling pathways invoked within seconds of a primary stimulus. For example, administration of an inventive compound in vivo or ex vivo provides a method to modify cellular behavior, the method comprising contacting cells (in vivo or ex vivo), whose behavior is to be modified, with an effective amount of an inventive compound or a pharmaceutical composition thereof wherein said method is a method to: (1) inhibit proliferation of tumor cells and said amount is sufficient to inhibit said proliferation; (2) suppress activation of T-cells by antigen or IL-2 stimulation, and said amount is sufficient to promote said activation; (3) suppress activation of monocyte/macrophage cells by endotoxin, TNF, IL-1 or GM-CSF stimulation and said amount is sufficient to suppress said activation; (4) suppress antibody production of B-cells in response to an antigen, IL-4 or CD40 ligand and said amount is sufficient to suppress said antibody production; (5) inhibit the proliferation of smooth muscle cells in response to growth factors capable of stimulating said proliferation and said amount is sufficient to inhibit said proliferation; (6) lower systemic vascular resistance conferred by endothelial cells and said amount is sufficient to reduce the release of hypertension-inducing substances; (7) lower systemic vascular resistance induced by endothelial cells and said amount is sufficient to enhance the release of anti-hypertensive substances; (8) lower expression of adhesion molecules induced by enhancers thereof, and said amount is sufficient to lower said expression; (9) suppress the activation of T-cells and macrophages by HIV and said amount is sufficient to suppress said activation thus inhibiting viral replication; (10) inhibit the proliferation of kidney mesangial cells in response to stimulation by IL-1 and/or MIP-1.alpha. and/or PDGF and/or FGF and said amount is sufficient to inhibit said proliferation; (11) enhance the resistance of kidney glomerular or tubular cells to cyclosporin A or amphotericin B and said amount is sufficient to enhance said resistance; (12) prevent the release of MIP-1.alpha. by IL-1, TNF, or endotoxin stimulated monocytes and macrophages; (13) prevent the release of platelet activating factor by IL-1, TNF, or endotoxin treated megakaryocytes, fibroblastic cells, and macrophages; (14) prevent the down-regulation of receptors for cytokines in TNF-treated hematopoietic progenitor cells and said amount is sufficient to prevent said down-regulation; (15) suppress the production of metalloproteases in IL-1-stimulated or TNF-stimulated glomerular epithelial cells or synovial cells and said amount is sufficient to enhance said production; (16) enhance the resistance of gastrointestinal or pulmonary epithelial cells to cytotoxic drugs or radiation and said amount is sufficient to enhance said resistance; (17) enhance the antitumor effect of a non-alkylating antitumor agent and said amount is sufficient to enhance said effect; (18) to inhibit the production of osteoclast activating factor in response to IL-1, and said amount is sufficient to inhibit said production; (19) inhibit degranulation in response to IgE, and said amount is sufficient to inhibit said degranulation; (20) enhance the release of adrenergic neural transmitters, dopamine, norepinephrine, or epinephrine, or the neurotransmitter, acetylcholine, and said amount is sufficient to enhance said release; (21) modulate the post-synaptic "slow current" effects of the adrenergic neurotransmitters dopamine, epinephrine, or norepinephrine, or the neurotransmitter acetylcholine, and said amount is sufficient to modulate such slow currents; (22) suppress signaling by neurotransmitters including acetyl choline, leuenkephalin and serotonin; or (23) increase seizure theshold.

Detailed Description Paragraph Right (42):
There are a series of in vitro assays that can be used to measure immunosuppressive activity of a particular compound. These assays are predictive models for treatment

or prevention of autoimmune diseases, such as diabetes, lupus, arthritis, and the like. A first assay measures immunosuppressive activity of a drug at the B cell level. Spleens from adult mice contain immature B cells that express surface IgM. Cross-linking the surface IgM with an anti-mu antibody results in B cell proliferation. Additionally, this activation results in an increased expression of interleukin-4 receptors(IL-4R) on the surface of such cells. IL-4 acts as a growth factor for B cells and will increase the amount of proliferation induced by anti-mu. In the first assay, a mixture of anti-mu and murine IL-4 is added to murine splenocytes to cause their proliferation. Mice spleens are obtained from adult mice and a single cell suspension is prepared in RPMI 1640 medium supplemented with 10% FCS. Cells (200,000) are plated into flat-bottomed wells and pre-incubated for 1-2 hours with various concentrations of drug or PBS if it is a control well. A mixture of anti-mu and murine is added to the wells at a final concentration of 5 .mu.g/ml anti-mu and 12.5 ng/ml IL-4 and plates are incubated for three days. Proliferation is determined on the third day with a pulse of tritiated thymidine. The IC50 concentration of a particular inventive compound is the concentration of the compound that results in a 50% inhibition of the proliferation obtained from the positive control.

Detailed Description Paragraph Right (61):
The inventive compounds provide a method for maintaining homeostasis in cells contacted by primary stimuli by mitigating the effects of these primary stimuli on the secondary signaling pathways invoked within seconds of a primary stimulus. For example, administration of an inventive compound in vivo or ex vivo provides a method to modify cellular behavior, the method comprising contacting cells (in vivo or ex vivo), whose behavior is to be modified, with an effective amount of an inventive compound or a pharmaceutical composition thereof. The method is a method to: (1) inhibit proliferation of tumor cells, (2) suppress activation of T-cells by antigen or IL-2 stimulation (3) suppress activation of monocyte/macrophage cells by endotoxin, TNF, IL-1 or GM-CSF stimulation, (4) suppress antibody production of B-cells in response to an antigen, IL-4 or CD40 ligand, (5) inhibit the proliferation of smooth muscle cells in response to growth factors capable of stimulating said proliferation (6) lower systemic vascular resistance conferred by endothelial cells, (7) lower systemic vascular resistance induced by endothelial cells, (8) lower expression of adhesion molecules induced by enhancers thereof, (9) suppress the activation of T-cells and macrophages by HIV, (10) inhibit the proliferation of kidney mesangial cells in response to stimulation by IL-1 and/or MIP-1.alpha. and/or PDGF and/or FGF, (11) enhance the resistance of kidney glomerular or tubular cells to cyclosporin A or amphotericin B, (12) prevent the release of MIP-1.alpha. by IL-1, TNF, or endotoxin stimulated monocytes and macrophages; (13) prevent the release of platelet activating factor by IL-1, TNF, or endotoxin treated megakaryocytes, fibroblastic cells, and macrophages; (14) prevent the down-regulation of receptors for cytokines in TNF-treated hematopoietic progenitor cells, (15) suppress the production of metalloproteases in IL-1-stimulated or TNF-stimulated glomerular epithelial cells or synovial cells, (16) enhance the resistance of gastrointestinal or pulmonary epithelial cells to cytotoxic drugs or radiation, (17) enhance the antitumor effect of a nonalkylating antitumor agent, (18) to inhibit the production of osteoclast activating factor in response to IL-1, (19) inhibit degranulation in response to IgE, (20) enhance the release of adrenergic neural transmitters, dopamine, norepinephrine, or epinephrine, or the neurotransmitter, acetylcholine, (21) modulate the post-synaptic "slow current" effects of the adrenergic neurotransmitters dopamine, epinephrine, or norepinephrine, or the neurotransmitter acetylcholine, (22) suppress signaling by neurotransmitters including acetyl choline, leuenkephalin and seretonin; or (23) increase seizure theshold.

Detailed Description Paragraph Right (141):
This example illustrates potential antigen specific anergy-induction of inventive compounds. Anergy, as used herein, is a prolonged state of T cell "unresponsiveness," due to T cell anitgen recognition (without co-stimulation) or induced proliferation blockage. This later T cell anergy may occur when a T cell's proliferation ability in response to IL-2 is blocked by some agent. Anergy is generally considered to be a type of tolerance to antigen activation. Thus, anergy is a means for predicting in vivo tolerance-enhancing agents. Tolerence is important in preventing organ rejection in tranplant procedures, as well as other autoimmune

diseases such as scleroderma, rheumatoid arthritis, lupus, and diabetes-related autoimmunity.

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L3: Entry 30 of 61 File: USPT Mar 2, 1999

DOCUMENT-IDENTIFIER: US 5877210 A
TITLE: Phosphotyrosine phosphatase inhibitors or phosphotyrosine kinase activators for controlling cellular proliferation

Detailed Description Paragraph Right (102):
However, phosphotyrosine phosphatase inhibitors can also be used to control proliferation of normal B cells, particularly in situations in which downregulation of the immune response is desired. Such situations include induction of immunosuppression to prevent transplant rejection, as well as in the treatment of autoimmune diseases such as rheumatoid arthritis, Hashimoto's thyroiditis, and systemic lupus erythematosus, as well as other autoimmune diseases.

Detailed Description Paragraph Right (116):
In particular, phosphotyrosine phosphatase inhibitors can be used to suppress the immune system in order to prevent organ and tissue rejection during transplantation and also in the treatment of autoimmune diseases such as rheumatoid arthritis, Hashimoto's thyroiditis, systemic lupus erythematosus, Guillain-Barre Syndrome, and possibly multiple sclerosis.

Detailed Description Paragraph Right (120):
Methods according to the present invention can further be used to prevent class-switching in antibodies from Ig or IgM to IgE. It is desirable to block IgE production because this type of antibody mediates many allergic responses, particularly immediate-type hypersensitivity reactions such as anaphylaxis, atopy, and urticaria. The CD40 ligand gp39 and the cytokine IL-4 act on B cells to induce the switching of the type of antibody produced from IgM to IgE. CD40 and IL-4 mechanisms of action are known to involve tyrosine phosphorylation. Phosphotyrosine phosphatase inhibitors such as BMLOV disrupt the normal pattern of tyrosine phosphorylation, thus disrupting the class-switching process. The administration of BMLOV, in particular, can markedly inhibit the production of IgE antibody while much less markedly inhibiting the production of IgG subclasses such as IgG1 and IgG4. This leads to the result that the ratio of IgG to IgE increases (Example 14). These results lead to the conclusion that phosphotyrosine phosphatase inhibitors such as BMLOV have value in the treatment of allergy.

Detailed Description Paragraph Right (177):
BMLOV can inhibit normal tonsillar B cell proliferation driven by stimulation of CD40 via either anti-CD40 antibody or gp39 ligand plus either anti-CD20 antibody or phorbol 12-myristate 13-acetate (PMA). In one experiment, doses of 0.1 to 10 .mu.M had little effect on proliferation (FIG. 3). In a second experiment, a dose of 5 .mu.M gave substantial inhibition of proliferation and a dose of 50 .mu.M completely blocked proliferation (FIG. 4). Variations between the individuals from which the tonsils were derived could account for the differences between these experiments.

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L2: Entry 25 of 96 File: USPT Sep 18, 2001

DOCUMENT-IDENTIFIER: US 6290972 B1
TITLE: Method of augmenting a vaccine response by administering CD40 ligand

Detailed Description Paragraph Right (29):
Both CD40 agonists and CD40 antagonists will have useful therapeutic activity. For example, CD40 agonists (i.e., membrane-bound CD40-L and oligomeric CD40-L) are useful as vaccine adjuvants and for stimulating mAb production from hybridoma cells. CD40 antagonists (i.e., CD40 receptor, CD40/Fc and possibly soluble, monomeric CD40-L) are useful for treating autoimmune diseases characterized by presence of high levels of antigenantibody complexes, such as allergy, systemic lupus erythematosis, rheumatoid arthritis, insulin dependent diabetes mellitus (IDDM), graft versus host disease (GVHD) and others.

Detailed Description Paragraph Right (115):
These data indicate that the interaction of CD40 with its ligand is the principal molecular interaction responsible for T cell contact dependent induction of B cell growth and differentiation to both antigen-specific antibody production and polyclonal Ig secretion. As such, these data suggest that antagonists of this interaction, by soluble CD40, CD40/Fc fusion protein and possibly soluble CD40-L (monomeric), will significantly interfere with development of antibody responses. Therefore clinical situations where CD40, CD40/Fc fusion proteins and soluble CD40-L are suitable include allergy, lupus, rheumatoid arthritis, insulin dependent diabetes mellitus, and any other diseases where autoimmune antibody or antigen/antibody complexes are responsible for clinical pathology of the disease. Moreover, membrane-bound CD40-L or oligomeric soluble CD40-L will be useful to stimulate B cell proliferation and antibody production. As such, these forms of CD40-L are most useful for vaccine adjuvants and as a stimulating agent for mAb secretion from hybridoma cells.

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L2: Entry 25 of 96 File: USPT Sep 18, 2001

US-PAT-NO: 6290972
DOCUMENT-IDENTIFIER: US 6290972 B1

TITLE: Method of augmenting a vaccine response by administering CD40 ligand

DATE-ISSUED: September 18, 2001

US-CL-CURRENT: 424/278.1; 435/440, 435/69.1, 514/2, 514/8, 514/885, 530/350, 536/23.1, 536/23.4, 536/23.5

APPL-NO: 8/ 770974 [PALM]
DATE FILED: December 19, 1996

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATION
This application is a divisional application of U.S. patent application Ser. No. 08/477,733, filed Jun. 7, 1995, now U.S. Pat. No. 5,981,724, which is a continuation-in-part application of U.S. patent application Ser. No. 08/249,189, filed May 24, 1994, now U.S. Pat. No. 5,961,974, which is a continuation-in-part of U.S. patent application Ser. No. 07/969,703, filed Oct. 23, 1992, now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 07/805,723, filed on Dec. 5, 1991, now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 07/783,707, filed on Oct. 25, 1991, now abandoned.

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L2: Entry 57 of 96 File: USPT May 11, 1999

DOCUMENT-IDENTIFIER: US 5902585 A
TITLE: Methods of inducing T cell unresponsiveness to donor tissue or organ in a recipient with GP39 antagonists

Abstract Paragraph Left (1):
Methods for inducing T cell tolerance to a tissue or organ graft in a transplant recipeint are disclosed. The methods involve administering to a subject: 1) an allogeneic or xenogeneic cell which expresses donor antigens and which has a ligand on the cell surface which interacts with a receptor on the surface of a recipient T cell which mediates contact-dependent helper effector function; and 2) an antagonist of the receptor which inhibits interaction of the ligand with the receptor. In a preferred embodiment, the allogeneic or xenogeneic cell is a B cell, preferably a resting B cell, and the molecule on the surface of the T cell which mediates contact-dependent helper effector function is gp39. A preferred gp39 antagonist is an anti-gp39 antibody. The allogeneic or xenogeneic cell and the gp39 antagonist are typically administered to a transplant recipient prior to transplantation of the tissue or organ. The methods of the invention can be used to induce T cell tolerance to transplants such as liver, kidney, heart, lung, sklin, muscle, neuronal tissue, stomach and intestine. A method for treating diabetes comprising administering to a subject allogeneic or xenogeneic cells expressing donor antigens, a gp39 antagonist and pancreatic islets is also disclosed.

Brief Summary Paragraph Right (4):
A molecule, CD40, has been identified on the surface of immature and mature B lymphocytes which, when crosslinked by antibodies, induces B cell proliferation. Valle et al., Eur. Immunol., 19:1463-1467 (1989); Gordon et al., J. Immuol., 140:1425-1430 (1988); Gruber et al., J. Immunol., 142: 4144-4152 (1989). CD40 has been molecularly cloned and characterized. Stamenkovic et al., EMBO J., 8:1403-1410 (1989). A ligand for CD40, gp39 (also called CD40 ligand or CD40L) has also been molecularly cloned and characterized. Armitage et al., Nature, 357:80-82 (1992); Lederman et al., J. Exp. Med., 175:1091-1101 (1992); Hollenbaugh et al., EMBO J., 11:4313-4319 (1992). The gp39 protein is expressed on activated, but not resting, CD4.sup.+ Th cells. Spriggs et al., J. Exp. Med., 176:1543-1550 (1992); Lane et al., Eur. J. Immunol., 22:2573-2578 (1992); Roy et al., J. Immunol., 151:1-14 (1993). Cells transfected with the gp39 gene and expressing the gp39 protein on their surface can trigger B cell proliferation and, together with other stimulatory signals, can induce antibody production. Armitage et al., Nature, 357:80-82 (1992); Hollenbauzh et al., EMBO J., 11:4313-4319 (1992).

Brief Summary Paragraph Right (7):
In a preferred embodiment, the receptor on the surface of a recipient T cell which mediates contact-dependent helper effector functions is gp39. In this embodiment, the antagonist is a molecule which inhibits the interaction of gp39 on a T cell with a gp39 ligand on an allogeneic or xenogeneic cell. A particularly preferred gp39 antagonist is an anti-gp39 antibody. In another embodiment, the gp39 antagonist is a soluble form of a gp39 ligand. for example soluble CD40. The allogeneic or xenogeneic cell which is administered to the recipient is preferably a lymphoid cell, for example a B cell. Alternatively, the allogeneic or xenogeneic cell is a small resting B cell. The allogeneic or xenogeneic cell and the antagonist (e.g., anti-gp39 antibody) are typically administered to a recipient subject prior to transplantation of the tissue or organ into the subject. For example, lymphoid cells (e.g., B cells) from the donor of the tissue or organ are administered to the recipient, together with the antagonist, prior to transplantation of the tissue or

organ into the recipient.

Brief Summary Paragraph Right (8):
The methods of the current invention can be used, for example, to induce T cell tolerance to transplanted tissue or organs such as liver, kidney, heart, lung, skin, muscle, neuronal tissue, stomach and intestines. In one embodiment, the transplanted tissue comprises pancreatic islets. Accordingly, the invention provides a method for treating diabetes comprising administering to a subject in need of treatment: 1) allogeneic or xenogeneic cells which express donor antigens; 2) an antagonist of a receptor on the surface of recipient T cells which mediates contact-dependent helper effector functions, such as a gp39 antagonist (e.g., an anti-gp39 antibody); and 3) donor pancreatic islets.

Drawing Description Paragraph Right (1):
FIG. 1 is a graphic representation of the survival of transplanted pancreatic islet allografts in chemically diabetic mice pretreated with anti-gp39 antibody alone or pretreated with unfractionated or fractionated allogeneic spleen cells alone.

Drawing Description Paragraph Right (2):
FIGS. 2A and 2B are graphic representations of the survival of transplanted pancreatic islet allografts, as measured by a decrease in plasma glucose concentration, in chemically diabetic mice pretreated with a single dose of fractionated allogeneic spleen cells together with an anti-gp39 antibody (MRI) treatment for either 2 weeks (panel A) or 7 weeks (panel B). Each curve represents data from an individual mouse. Open symbols identify recipients in which the islet allograft failed spontaneously. Closed symbols indicate mice whose islet grafts were functional at the termination of the experiment.

Detailed Description Paragraph Right (4):
According to the methods of the invention, a gp39 antagonist is administered to a recipient to interfere with the interaction of gp39 on recipient T cells with a gp39 ligand on an allogeneic or xenogeneic cell, such as a B cell, administered to the recipient. A gp39 antagonist is defined as a molecule which interferes with this interaction. The gp39 antagonist can be an antibody directed against gp39 (e.g., a monoclonal antibody against gp39), a fragment or derivative of an antibody directed against gp39 (e.g., Fab or F(ab)'2 fragments, chimeric antibodies or humanized antibodies), soluble forms of a gp39 ligand (e.g., soluble CD40), soluble forms of a fusion protein of a gp39 ligand (e.g., soluble CD40Ig), or pharmaceutical agents which disrupt or interfere with the gp39-CD40 interaction.

Detailed Description Paragraph Right (5):
A mammal, (e.g., a mouse, hamster, or rabbit) can be immunized with an immunogenic form of gp39 protein or protein fragment (e.g., peptide fragment) which elicits an antibody response in the mammal. A cell which expresses gp39 on its surface can also be used as the immunogen. Alternative immunogens include purified gp39 protein or protein fragments. gp39 can be purified from a gp39-expressing cell by standard purification techniques. Additionally, gp39 cDNA (Armitage et al., Nature, 357:80-82 (1992); Lederman et al., J. Exp. Med., 175:1091-1101 (1992); Hollenbaugh et al., EMBO J., 11:4313-4319 (1992)) can be expressed in a host cell, e.g., bacteria or a mammalian cell line, and gp39 protein purified from cell cultures by standard techniques. Alternatively, gp39 peptides can be synthesized based upon the amino acid sequence of gp39 (disclosed in Armitage et al., Nature, 357:80-82 (1992); Lederman et al., J. Exp. Med., 175:1091-1101 (1992); Hollenbaugh et al., EMBO J., 11:4313-4319 (1992)) using known techniques (e.g. F-moc or T-boc chemical synthesis). Techniques for conferring immunogenicity on a protein include conjugation to carriers or other techniques well known in the art. For example, the protein can be administered in the presence of adjuvant. The progress of immunization can be monitored by detection of antibody titers in plasma or serum. Standard ELISA or other immunoassay can be used with the immunogen as antigen to assess the levels of antibodies.

Detailed Description Paragraph Right (7):
The term antibody as used herein is intended to include fragments thereof which are specifically reactive with a gp39 protein or peptide thereof or gp39 fusion protein. Antibodies can be fragmented using conventional techniques and the fragments

screened for utility in the same manner as described above for whole antibodies. For example, F(ab').sub.2 fragments can be generated by treating antibody with pepsin. The resulting F(ab').sub.2 fragment can be treated to reduce disulfide bridges to produce Fab' fragments. The antibody of the present invention is further intended to include bispecific and chimeric molecules having an anti-gp39 portion.

Detailed Description Paragraph Right (8):
When antibodies produced in non-human subjects are used therapeutically in humans, they are recognized to varying degrees as foreign and an immune response may be generated in the patient. One approach for minimizing or eliminating this problem, which is preferable to general immunosuppression, is to produce chimeric antibody derivatives, i.e., antibody molecules that combine a non-human animal variable region and a human constant region. Chimeric antibody molecules can include, for example, the antigen binding domain from an antibody of a mouse, rat, or other species, with human constant regions. A variety of approaches for making chimeric antibodies have been described and can be used to make chimeric antibodies containing the immunoglobulin variable region which recognizes gp39. See, for example, Morrison et al., Proc. Natl. Acad. Sci. USA. 81:6851 (1985); Takeda et al., Nature 314:452 (1985), Cabilly et al., U.S. Pat. No. 4,816,567; Boss et al., U.S. Pat. No. 4,816,397; Tanaguchi et al., European Patent Publication EP171496; European Patent Publication 0173494, United Kingdom Patent GB 2177096B. It is expected that such chimeric antibodies would be less immunogenic in a human subject than the corresponding non-chimeric antibody.

Detailed Description Paragraph Right (9):
For human therapeutic purposes the monoclonal or chimeric antibodies specifically reactive with a gp39 protein or peptide can be further humanized by producing human variable region chimeras, in which parts of the Evariable regions, especially the conserved framework regions of the antigen-binding domain, are of human origin and only the hypervariable regions are of non-human origin. Such altered immunoglobulin molecules may be made by any of several techniques known in the art, (e.g., Teng et al., Proc. Natl. Acad. Sci. U.S.A., 80:7308-7312 (1983); Kozbor et al., Immunology Today, 4:7279 (1983); Olsson et al., Meth. Enzymol., 92:3-16 (1982)), and are preferably made according to the teachings of PCT Publication W092/06193 or EP 0239400. Humanized antibodies can be commercially produced by, for example, Scotgen Limited, 2 Holly Road, Twickenham, Middlesex, Great Britain.

Detailed Description Paragraph Right (10):
Another method of generating specific antibodies, or antibody fragments, reactive against a gp39 protein or peptide is to screen expression libraries encoding immunoglobulin genes, or portions thereof, expressed in bacteria w ith a gp39 protein or peptide. For example, complete Fab fragments, VH regions and FV regions can be expressed in bacteria using phage expression libraries. See for example Ward et al., Nature, 341: 544-546: (1989); Huse et al., Science, 246: 1275-1281 (1989); and McCafferty et al., Nature, 348: 552-554 (1990). Screening such libraries with, for example, a gp39 peptide can identify immunoglobin fragments reactive with gp39. Alternatively, the SCID-hu mouse (available from Genpharm) can be used to produce antibodies, or fragments thereof.

Detailed Description Paragraph Right (11):
Methodologies for producing monoclonal antibodies directed against gp39, including human gp39 and mouse gp39, and suitable monoclonal antibodies for use in the methods of the invention, are described in further detail in Example 2.

Detailed Description Paragraph Right (17):
T cell tolerance to an organ or tissue graft can be induced according to the invention by administration to the transplant recipient of a gp39 antagonist in conjunction with an allogeneic or xenogeneic cell which expresses donor antigens and interacts with recipient T cells via gp39. In a preferred embodiment, the allogeneic or xenogeneic cell and the gp39 antagonist are administered to the recipient simultaneously or contemporaneously. Alternatively, the gp39 antagonist can be administered prior to administering the allogeneic or xenogeneic cells, for example when the antagonist is an antibody with a long half-life. In a preferred embodiment, the antagonist and the allogeneic or xenogeneic cells are admininstered to the recipient prior to transplantation of the organ or tissue into the recipient (i.e.,

the recipient is pretreated with the antagonist and cells). For example, administration of the allogeneic or xenogeneic cells and antagonist can be performed several days (e.g., five to eight days) prior to tissue or organ transplantation.

Detailed Description Paragraph Right (19):
An antagonist of the invention is administered to a subject in a biologically compatible form suitable for pharmaceutical administration in vivo to induce T cell tolerance. By "biologically compatible form suitable for administration in vivo" is meant a form of the antagonist to be administered in which any toxic effects are outweighed by the therapeutic effects of the compound. The term subject is intended to include living organisms in which an immune response can be elicited, e.g., mammals. Examples of subjects include humans, dogs, cats, mice, rats, and transgenic species thereof. A gp39 antagonist of can be administered in any pharmacological form, optionally with a pharmaceutically acceptable carrier. Administration of a therapeutically active amount of the antagonist is defined as an amount effective, at dosages and for periods of time necessary to achieve the desired result (e.g., T cell tolerance). For example, a therapeutically active amount of an antagonist of gp39 may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antagonist to elicit a desired response in the individual. Dosage regimens may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. As described in Example 1 for treatment with an anti-gp39 antibody, an effective treatment regimen can include initiation of antibody administration prior to tissue or organ transplantation (e.g., five to eight days before transplantation), followed by readministration of the antibody (e.g., every other day) for several weeks (e.g. two to seven weeks) after transplantation.

Detailed Description Paragraph Right (28):
The methods of the invention are applicable to a wide variety of tissue and organ transplant situations. The methods can be used to induce T cell tolerance in a recipient of a graft of a tissue or organ such as pancreatic islets, liver, kidney, heart, lung, skin, muscle, neuronal tissue, stomach and intestines. Thus, the methods of the invention can be applied in treatments of diseases or conditions which entail tissue or organ transplantation (e.g., liver transplantation to treat hypercholesterolemia, transplantation of muscle cells to treat muscular dystrophy, transplantation of neuronal tissue to treat Huntington's disease or Parkinson's disease etc.). In a preferred embodiment, the transplanted tissue comprises pancreatic islets. Accordingly, the invention encompasses a method for treating diabetes by pancreatic islet cell transplantation. The method comprises administering to a subject in need of treatment: 1) allogeneic or xenogeneic cells which express donor antigens, 2) an antagonist of a molecule expressed on recipient T cells which mediates contact-dependent helper effector function, such as a gp39 antagonist (e.g., anti-gp39 antibody) and 3) donor pancreatic islet cells. Preferably, the allogeneic or xenogeneic cells and the antagonist are administered to the recipient prior to administration of the pancreatic islets.

Detailed Description Paragraph Right (30):
Contemporary allotransplantation studies depend on generalized immunosuppression that non-specifically ablates immune effector functions. However, immunosuppressive pharmaceuticals can cause significant side effects. In addition, allotransplantation of islet of Langerhans for the treatment of diabetes has proven refractory to this approach (see e.g. Robertson, R. P. (1992) N. Engl. J. Med 327, 1861). Therapies with antibodies directed against T cells may allow successful allografting of islets in rodents, but this approach too uniformly results in generalized immunosuppression (Carpenter, C. B. (1990) N. Engl. J. Med. 322, 1224; Roark, J. H. et al. (1992) Transplantation 54, 1098; Kahan, B. D. (1992) Curr. Opin. Immunol. 4, 553). In this example, tolerance to islet allografts was induced in a transplant recipient by manipulating the presentation of alloantigen to T cells so as to prevent their activation. The survival of islet allografts in chemically diabetic C57BL/6 (H-2b) mice was examined using the following methodology:

Detailed Description Paragraph Right (31):
Male C57BI/6J (H-2b) mice were rendered diabetic by the intravenous administration of streptozotocin (140 mg/kg). Permanent diabetes was confirmed by the demonstration

of a plasma glucose concentration.gtoreq.400 mg/dl on three occasions over a period of one week.

Detailed Description Paragraph Right (33):
Graft recipients were pretreated with either unfractionated (C57.times.BALB/c)F.sub.1 (H-2.sup.b/d) allogeneic spleen cells, elutriated "fraction 19" small diameter spleen cells that had been depleted of APC activity (isolated as described above), an anti-gp39 monoclonal antibody (MR1, see Example 2, Experiment 3), or a combination of allogeneic cells and anti-gp39 antibody. The fraction 19 cells were tested at two different dose ranges, a low dosage of 40-44.times.10.sup.6 cells or a high dose of 77-88.times.10.sup.6 cells. Control animals received neither allogeneic cells nor antibody treatment. Allogeneic cells were administered to graft recipients by tail vein injection five to eight days prior to islet allograft transplantation. MR1 antibody treatment was at a dose of 250 .mu.g/mouse twice weekly beginning 7 days before islet transplantation and continuing for 2-7 weeks or until graft failure. The first injection of antibody was typically given on the same day as the first injection of allogeneic spleen cells.

Detailed Description Paragraph Right (34):
Allogeneic BALB/c (H-2.sup.d) islets were isolated by a modified collagenase digestion method (Gottlieb, P. A. et al. (1990) Diabetes 39, 643). Islets at a dose of 30 islets/g body weight were implanted into the subrenal capsule of the recipient C57B1/6J (H-2.sup.b) mice immediately after isolation. Graft survival was defined as the maintenance of a plasma glucose concentration.ltoreq.200 mg/dl.

Detailed Description Paragraph Right (35):
In a first series of experiments, islet allograft recipients were pretreated with either allogeneic spleen cells alone or anti-gp39 antibody alone. As shown in FIG. 1, in the absence of spleen cell pretreatment, all islet allografts were rejected within 13 days of transplantation (9.+-.2 d; range 5-13 d; N=23). Poor islet survival was also observed in animals treated only with unfractionated spleen cells containing normal APC activity (6.+-.3 d; range 4-12 d; N=7) or low doses (40-44.times.10.sup.6 cells) of Fraction 19 APC depleted spleen cells (7.+-.3 d; range 3-14 d , N=16). In contrast, injection of a higher dose of Fraction 19 APC-depleted small splenocytes (75-88.times.10.sup.6 cells) prolonged allograft survival (19+10 d; range 7-40 d: N=16). This effect on the duration of graft survival was statistically significant (F.sub.3.58 =17.3 p<0,001 when compared with groups treated with nothing, whole spleen transfusions. or the lower dose of fraction 19 spleen cells) but was not permanent. The extended but finite survival of allogeneic islets in diabetic recipients of APC depleted, fraction 19 small cells suggested that these cells alone cannot sustain allograft survival. An additional cohort of graft recipients was treated with 77-88.times.10.sup.6 fraction 20 cells. This fraction was also composed overwhelmingly of small lymphocytes but differs from the fraction 19 population in that it contains measurable APC function. Recipients of these cells (N=6) all rejected their grafts promptly (mean=8.5 d, range 6-12). Another group of graft recipients was treated solely with an anti-gp39 monoclonal antibody, MR1. FIG. 1 illustrates that islet allograffs failed within 15 days in 7/11 mice treated only with the anti-gp39 mAb. The remaining four mice had functional grafts at the conclusion of the experiment on day 48. The results demonstrate that administration to the recipient of the MR1 anti-gp39 antibody alone can prolong islet allograft survival (mean 20=19 d; range 9 indefinite: N=5). The degree of prolongation was statistically similar to that achieved using a higher dose of Fraction 19 spleen cells alone and significantly longer than that achieved in the other three groups (p<0.05).

Detailed Description Paragraph Right (38):
Islet allografts and the native pancreas were studied histologically in all animals, either when the graft failed or at the end of the experiment. Histological sections of islet allografts in the kidneys of recipients of fractionated allogeneic small lymphocytes and continuous (7 weeks) MRI mAb treatment displayed abundant intact islets visible below the renal capsule which were devoid of mononuclear infiltration and contained well granulated insulin and glucagon positive cells. In contrast, histological sections of islet allografts in the kidneys of recipients treated with anti-gp39 mAb alone showed characteristic intense mononuclear cell inflammation and attendant islet cell destruction. In all host pancreata, islet morphology was

uniformly consistent with streptozotocin diabetes.

Detailed Description Paragraph Right (39):
For induction of antigen-specific T cell tolerance in a human subject, it is preferable to administer an antibody directed against human gp39. The following methodology was used to produce mouse anti-human gp39 monoclonal antibodies. Balb/c mice were immunized with a soluble gp39 fusion protein, gp39-CD8, in Complete Freund's Adjuvant (CFA). Mice were subsequently challenged 6 weeks later with soluble gp39-CD8 in Incomplete Freund's Adjuvant (IFA). Soluble gp39-CD8 was given in soluble form 4 weeks after secondary immunization. Mice were then boosted with activated human peripheral blood lymphocytes 2 weeks later, followed by a final boost with soluble gp39-CD8 after an additional 2 weeks. Splenocytes were fused with the NS-1 fusion partner on day 4 after final immunization as per standard protocols.

Detailed Description Paragraph Right (40):
Clones producing anti-human gp39 antibodies were selected based on a multiple screening process. Clones were initially screened by a plate binding assay using gp39-CD8. Positive clones were then screened against a control CD8 fusion protein, CD72-CD8. Clones which scored positive on the CD8-CD72 plate binding assay were eliminated. The remaining clones were subsequently screened on resting and 6 hour activated human peripheral blood lymphocytes (PBL) by flow cytometric analysis. Hybridomas staining activated. but not resting, PBL were considered positive. Finally, the remaining clones were tested for their ability to block the binding of CD40Ig to plate bound gp39.

Detailed Description Paragraph Right (42):
A similar immunization procedure to that described in Experiment 1 was used to produce additional antibodies directed against human gp39. One Balb/c mouse was immunized with soluble gp39-CD8 in CFA, followed by challenge with 6 hour activated human peripheral blood lymphocytes 4 weeks later. The mouse was subsequently boosted with soluble gp39-CD8 4 days prior to fusion of splenocytes with the NS-1 fusion partner per standard protocols. Screening of hybridoma clones was performed by flow cytometric staining of 6 hour activated human PBLs. Clones staining activated but not resting human PBLs were selected for subsequent analysis. Two clones, 4D9-8 and 4D9-9 were selected.

Detailed Description Paragraph Right (43):
The specificity of the selected antibodies was confirmed by several assays. First, flora cytometric analysis demonstrated that 4D9-8 and 4D9-9 stain activated, but not resting peripheral blood T cells (see FIG. 3). Expression of the molecule recognized by these antibodies is detectable within 4 hours of activation, is maximal between 6-8 hours after activation, and is undetectable by 24 hours after activation. 4D9-8 and 4D9-9 recognize a molecule expressed on activated CD3+ PBLs, predominantly of the CD4.sup.+ phenotype, but a portion of CD8.sup.+ T cells also express the molecule. Expression of the molecule recognized by these mAbs is inhibited by the presence of cyclosporin A in the culture medium, as is the expression of gp39 (see FIG. 4). The kinetics and distribution of expression of the molecule recognized by these mAbs are identical to that of gp39, as detected by the fusion protein of human CD40Ig. In addition, 4D9-8 and 4D9-9 block the staining of gp39 by CD40Ig (see FIG. 5). In an ELISA assay, 4D9-8 and 4D9-9 both recognize gp39-CD8, a soluble fusion form of the gp39 molecule. Moreover, 4D9-8 and 4D9-9 both immunoprecipitate a molecule of approximately 36 kd from .sup.35 S-methionine labeled activated human PBLs. The immunoprecipitated molecule is identical to that precipitated by the human CD40Ig fusion protein.

Detailed Description Paragraph Right (44):
The functional activity of 4D9-8 and 4D9-9 was assayed as follows. First, the ability of the mAbs to inhibit the proliferation of purified human B cells cultured with IL-4 and soluble gp39 was measured. Purified human B cells were cultured with gp39 and IL-4 in the presence or absence of purified monoclonal antibodies or CD40Ig at dosages between 0 and 50 mg/ml. B cell proliferation was determined after 3 days in culture by thymidine incorporation. The results (FIG. 6) demonstrate that both 4D9-8 and 4D9-9 can inhibit B cell proliferation induced by gp39 and IL-4. Next, the ability of the mAbs to inhibit B cell differentiation, as measured by Ig production

induced by anti-CD3 activated T cells and IL-2. Purified human B cells were cultured with anti-CD3 activated human T cells and IL-2 for 6 days in the presence or absence of purified monoclonal antibodies or CD40Ig as dosages between 0 and 50 mg/ml. IgM production was assessed by ELISA on day 6. The results (FIG. 7) demonstrate that both antibodies can inhibit T cell dependent B cell differentiation.

Detailed Description Paragraph Right (45):
In one embodiment of the invention, the gp39 antagonist is an anti-mouse gp39 monoclonal antibody, MR1. The following method was used to produce the MR1 monoclonal antibody, and may be used to generate other antibodies directed toward gp39.

Detailed Description Paragraph Left (7):
Induction of Diabetes

Detailed Description Paragraph Left (12):
Experiment 1--Antibodies directed against human gp39

Detailed Description Paragraph Left (13):
Experiment 2--Antibodies directed against human gp39

Detailed Description Paragraph Left (14):
Experiment 3--Antibodies directed against mouse gp39

Detailed Description Paragraph Center (5):
Production and Characterization of Anti-gp39 Antibodies

CLAIMS:

1. A method for inducing T-cell non-responsiveness to a donor tissue or organ in a recipient of a tissue or organ comprising administering to a recipient which has or is to become transplanted with an allogeneic or xenogeneic cell that expresses at least one donor antigen and also expresses gp39 ligand on a cell surface thereof, an amount of a gp39 antagonist sufficient to induce T-cell non-responsiveness to said donor tissue or organ, wherein said gp39 antagonist is selected from the group consisting of anti-gp39 antibodies and fragments thereof that specifically bind gp39, soluble CD40 and soluble CD40 fusion proteins.

2. The method of claim 1, wherein the gp39 antagonist is an anti-gp39 antibody.

3. The method of claim 2, wherein the anti-gp39 antibody is a monoclonal antibody.

4. The method of claim 2, wherein the anti-gp39 antibody is a anti-human gp39 antibody.

13. A method for inducing T-cell non-responsiveness to a donor tissue or organ in a recipient of the tissue or organ comprising administering to a recipient which has or is to become transplanted with an allogeneic or xenogeneic cell which expresses at least one donor antigen an effective amount of a gp39 antagonist selected from the group consisting of anti-gp39 antibodies and fragments thereof that specifically bind gp39, soluble CD40 and soluble CD40 fusion proteins, wherein the amount is effective to induce T-cell non-responsiveness to a transplanted donor tissue or organ.

14. The method of claim 13, wherein the gp39 antagonist is an anti-gp39 antibody.

15. The method of claim 14, wherein the anti-gp39 antibody is a monoclonal antibody.

16. The method of claim 14, wherein the anti-gp39 antibody is an anti-human gp39 antibody.

27. A method for inducing T-cell non-responsiveness to a donor tissue or organ in a recipient of the tissue or organ comprising administering to a recipient which has or is to become trasplanted into to a donor allogeneic cell, an effective amount of

an anti-gp39 antibody or fragment thereof that specifically binds gp 39, wherein the effective amount refers to an amount sufficient to induce T-cell non-responsiveness to a transplanted allogeneic donor tissue or organ.

28. The method of claim 27, wherein the anti-gp39 antibody is a monoclonal antibody.

29. The method of claim 28, wherein the anti-gp39 antibody is an anti-human gp39 antibody.